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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,048	01/26/2006	Philipp Hadwiger	A2038-7052US	3878
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ALNYLAM/FENWICK SILICON VALLEY CENTER 801 CALIFORNIA STREET MOUNTAIN VIEW, CA 94041				
EXAMINER				
CHONG, KIMBERLY				
ART UNIT		PAPER NUMBER		
1635				
NOTIFICATION DATE		DELIVERY MODE		
11/12/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/543,048

Applicant(s)

HADWIGER ET AL.

Examiner

KIMBERLY CHONG

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 86, 94-98, 100-102 and 110-119 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 86, 94-98, 100-102, 110-119 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 06/19/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/19/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. With entry of the amendment filed on 06/19/2009, claims 86, 94-98, 100-102, and 110-119 are pending in the application. Applicant has canceled claims 1-85, 87-93, 99 and 103-109.

Response to Applicant's Arguments

Claim Rejections - 35 USC § 103

The rejection of claims 86, 100-102, and 110-119 under 35 U.S.C. 103(a) as being unpatentable over Kay et al. et al. (US 2003/0139363), Fosnaugh et al. (US 2003/0143732), Frecht et al. (US Patent No. 7,097,856) and Florence et al. (Journal of Controlled Release, 2000, Vol. 65: 253-259 of record 08/22/2007) is maintained for the reasons of record.

The rejection of claims 86, 94-98 and 110-119 under 35 U.S.C. 103(a) as being unpatentable over Kay et al. et al. (US 2003/0139363), Fosnaugh et al. (US 2003/0143732), Manoharan, M. (20030064492, "Manoharan I") and Cook et al. (U.S.

Patent No. 6,803,198) and evidenced by Manoharan, M. (Applicant's IDS 02/13/2006, "Manoharan II") is maintained for the reasons of record.

Applicant's arguments filed 06/19/2009 have been fully considered but they are not persuasive. Applicant argues the prior art teach the 5' end of the antisense strand should contain a free OH group and point to Rana as well as references cited on pages 17-18 of the instant specification. Applicant argues that the prior art should be considered as a whole and one of ordinary skill in the art would follow the clear teachings of Rana such as Example IV and the references cited in the specification which teach that at the time of filing, dsRNA with 5' modifications in the antisense strand were unable to cause RNA interference. Further, it is argued by Applicant that Fosnaugh et al. only provide a general teaching of the generic possible configurations of siRNA conjugates and none of the cited references specifically teach a dsRNA conjugate wherein the lipophilic group is covalently attached to the 5' end of the complementary strand. Applicants argue that the instant specification highlights the importance of the phosphodiester linkage which is not evident in the art of record.

A careful reading of Rana would lead the skilled artisan to conclude that Rana do not teach away from covalently attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA. A summary of the examples disclosed in Rana is provided below in paragraph [0272]:

[0272] Recent studies have shown that synthetic siRNAs containing 5'-OH termini can successfully induce RNAi effects in Drosophila embryo lysates (Elbashir et al., 2001c; Nykanen et al., 2001) and cultured mammalian cells (Elbashir et al., 2001a). A model involving a 5' end kinase activity necessary for RNA interference has been proposed (Nykanen et al., 2001). However, there is no evidence that the 5' end hydroxyl is required for in vivo interference activity. The above results show that

replacing the 5' OH, a kinase target site, with amino groups inhibited RNAi activity. Further isolation of siRNA by biotin pull out experiments revealed that prior phosphatase activity was required for in vitro 5' end radiolabeling by a polynucleotide kinase. Taken together, these results provide strong evidence for the requirement of 5' end kinase activity for RNA interference effects in vivo.

From the studies of Rana and the early prior art on the importance of the 5' end hydroxyl of the antisense strand of a dsRNA, the teachings provide strong evidence that there was a requirement for the 5' end kinase activity for RNAi in vivo however there was "no evidence that the 5' end hydroxyl is required for in vivo interference activity." In other words, at the time of filing of the instant invention it was recognized that the 5' end of the antisense strand of a dsRNA would need to be amenable to 5' end kinase activity but did not necessarily require the OH group present.

This fact has been clearly demonstrated by Schwarz et al., a reference identified by Applicant for the assertion that a free OH must be present on the 5' end of the antisense strand (cited on page 17 of the specification and on the IDS filed 02/13/2006). Schwarz et al. teach that a dsRNA wherein the 5' end of the antisense strand was linked with a 6-amino-hexyl phosphoester was capable of RNAi (see page 544). Therefore, contrary to Applicant's arguments, it was known in the prior art that the 5' end of the antisense strand of a dsRNA did not require a free OH for RNAi and in fact was able to reduce gene expression wherein the 5' end was linked with a phosphodiester group.

Therefore, because the claimed oligonucleotide conjugates were known in the art at the time of the invention of the instantly claimed invention and because such conjugates were known to efficiently improve the cellular delivery of oligonucleotides and increase their affinity for the target gene as well as increase their resistance to

nucleases, it would have been obvious to one skilled in the art to use the conjugates taught by Frecht et al., Manoharan et al. and Cook et al. to achieve the predictable result of improvement in cellular delivery of siRNA molecules. Given there are a finite number of identified, predictable solutions such as attaching the lipophilic group to either of 4 positions total (the 5' or 3' end of the antisense strand or the 5' or 3' end of the sense strand) using phosphodiester linkages, a person of ordinary skill in the art has good reason to pursue the known methods of conjugation of nucleic acids which is a matter of routine experimentation, it would have been obvious to covalently link the lipophilic groups to either the 5' or 3' end of a dsRNA and use linkages such as a phosphodiester group as taught by Fosnaugh et al.

It must be noted that claims 112 and 113 are drawn to attachment of the lipophilic group to the 3' end of the sense strand and Applicant has not provided any arguments as to why this limitation would not be obvious in view of the previous rejection.

Priority

It must be noted that the claimed subject matter drawn to a dsRNA comprising a lipophilic group having a logKow exceeding 1, 1.5, 2 or 3 wherein the linkage comprises a phosphodiester group does not appear to be supported by the translated German document (Transtek Document No. GE0204) filed on 02/22/2008. Moreover, this document is not annotated to clearly correspond to the Foreign Priority document filed

as Germany 10302121.2, if that was Applicant's intent. The priority of the instant claims is not at issue with regard to the rejection of record.

Prior Art Made of Record

The following reference is made of record but has not been used in any previous rejections of record:

Troy et al. (US 2004/0147027)

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-

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3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Tracy Vivlmore at 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
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